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Adverse Effects of ACE Inhibitors in Patients with Chronic Heart Failure and/or Ventricular Dysfunction

Meta-Analysis of Randomised Clinical Trials

Antònia Agustí, Sara Bonet, Josep Mª Arnau, Xavier Vidal and *Joan-Ramon Laporte*

Fundació Institut Català de Farmacologia; Servei de Farmacologia Clínica, Hospital Universitari Vall d'Hebron, and Department of Pharmacology, Therapeutics and Toxicology, Universitat Autònoma de Barcelona, Barcelona, Spain

Abstract

Background: The evidence-based benefit/risk evaluation of therapeutic interventions in randomised clinical trials should include both the assessment of the benefits and of the adverse outcomes. There is ample evidence that ACE inhibitors improve the symptoms and prognosis of chronic heart failure (CHF) and ventricular dysfunction. However, there is little systematic information on the tolerability and adverse effects associated with their use in these conditions.

Objective: To estimate the adverse events related to ACE inhibitor use in the treatment of CHF and ventricular dysfunction.

Design and Methods: Description of adverse events in reports of randomised clinical trials of ACE inhibitors in CHF or ventricular dysfunction was examined, and a meta-analysis was performed. Trials were included if they were placebo- or standard treatment-controlled, and if the treatment duration was at least 8 weeks. Relative risks and their 95% CIs were estimated with a random effects model.

Results: Only 22 (43%) of 51 original reports contained information on the number of withdrawals and their causes. Missing information from the remaining 29 trials was obtained from the authors. The weighted mean duration of treatment was 100.2 weeks. After excluding administrative reasons, heart failure, myocardial infarction and hypertension, the withdrawal rates attributed to adverse events were 13.8% and 9.4% for the ACE inhibitor and control groups, respectively (RR = 1.54 [95% CI 1.30–1.83]; weighted difference = 3.1 per 100 treated patients [95% CI 1.8–4.4]). Cough, hypotension, renal dysfunction, dizziness, hyperkalaemia, and impotence were all significantly more prevalent among patients treated with ACE inhibitors than among those in the control groups.

Conclusions: Among patients with CHF or ventricular dysfunction enrolled in randomised clinical trials, treatment with an ACE inhibitor for an average of 2 years leads to an additional 3% of treatment withdrawals. In a significant propor-

tion of the reports on these randomised clinical trials, information on adverse events leading to treatment withdrawal was inadequate. Proper evidence-based evaluation of the benefit/risk of therapeutic interventions needs a more systematic approach to reporting of adverse events experiences recorded in clinical trials.

In the last two decades, ACE inhibitors have become a cornerstone in the treatment of a wide spectrum of patients with chronic heart failure (CHF) or ventricular dysfunction. A recent meta-analysis including 39 trials in heart failure showed a decrease of 17% in mortality, which was more pronounced among high-risk patients.[1] On the other hand, various drug utilisation studies have suggested underuse of these drugs in the treatment of CHF in usual practice.[2-4] Although various reasons for this underuse have been given, it has been suggested that it could be related with fear of various adverse effects, such as hypotension, hyperkalaemia, and worsening of renal function.[5,6] Systematic information on the tolerability and adverse events of ACE inhibitors in patients with CHF may contribute to a better knowledge of the benefit-risk ratio of these drugs in this indication. However, apart from an overview of the two Studies of Left Ventricular Dysfunction (SOLVD) trials, where the incidence of adverse events and the reasons for withdrawals during long-term treatment[7] and during dose titration[8] were given, there is little systematic information on the tolerability and adverse events related to ACE inhibitors in patients with CHF.

With the aim of estimating the frequency and the reasons for withdrawal among patients randomised to treatment with ACE inhibitors, this information was collected and a meta-analysis was performed for withdrawals attributed to adverse events.

Study Design and Methods

Clinical trials were identified through bibliographic searches in computerised databases such as Medline (from January 1966 to December 1999) and EMBASE (from January 1974 to December 1999), and through manual search from the reference lists of the reports on clinical trials and reviews on the treatment of CHF and ventricular dysfunction after a myocardial infarction. In addition, a letter was sent to the first authors of the identified clinical trials, to experts in CHF and to the medical directors of pharmaceutical companies marketing ACE inhibitors, where we asked about any unpublished or unknown clinical trials with ACE inhibitors in the treatment of CHF and/or ventricular dysfunction.

Clinical trials were included in the meta-analysis if they were randomised, the use of an ACE inhibitor by the oral route was evaluated in patients with CHF or with ventricular dysfunction after a myocardial infarction, a control group treated with placebo or with standard treatment was included, the design was parallel or crossover (of these, only the results of the first phase before the crossover were considered), they gave information on patient withdrawals, and if they lasted for ≥8 weeks. Trials with and without a run-in period with ACE inhibitors or a test-dose before randomisation were included.

Three researchers (AA, JMA, XV) independently and blindly (with respect to the title, author and journal) evaluated each trial with regard to the inclusion criteria. Differences were resolved by consensus. In the majority of cases, the information on each trial was obtained from the published report. For each trial, two researchers (SB and AA) independently extracted the following information by means of a structured questionnaire: sex, age, New York Heart Association (NYHA) functional class, ejection fraction, concomitant treatments, primary endpoint and study duration, the particular ACE inhibi-

tor evaluated in the trial, and the number and reasons for withdrawals during the open pre-randomisation phase and during the post-randomisation phase. When information on any of these variables was not found in the report, the principal investigator was approached and asked to provide it. In the cases where it could not be obtained, the trial was excluded from the analysis for that particular variable.

In order to evaluate withdrawals due to adverse events related to ACE inhibitors, the reasons for withdrawals were examined. First, administrative causes (i.e. patient decision, recommendation by physician and/or nurse, protocol violation, or lack of adherence) were considered and excluded. Second, withdrawals due to events supposedly prevented by ACE inhibitors (e.g. worsening of CHF, myocardial infarction, and hypertension) were removed. The difference between the rates of withdrawals from other causes in each of the two groups was considered to be the best estimate of the true incidence of adverse effects attributable to ACE inhibitors leading to withdrawals.

In order to evaluate the effect of dose on the rate of withdrawals attributed to adverse drug events, information on the target daily dose and on the doses of ACE inhibitors actually taken by the participants was examined.

Possible heterogeneity of the treatment effect among the different studies was evaluated with the χ^2 test for heterogeneity.[9] Relative risks (RR) and their 95% CIs were estimated with the method of random effects by DerSimonian and Laird, with the Revman programme (version 4.0) developed by the Cochrane Collaboration.[10] The random effects model was chosen because, in the absence of heterogeneity, the results are similar to those obtained with the fixed effect model; they are also more generalisable and more conservative. The number of patients needed to treat in order to produce a withdrawal attributed to an adverse drug event was calculated as the inverse of the pooled differences between the rate of events (withdrawals) in the control group and the rate of events in the intervention group in each study.[11]

Results

Clinical Trials Included in the Meta-Analysis

Eighty-seven studies[12-98] were identified and assessed, 51[12-62] of which met the pre-established inclusion criteria (six unpublished trials).[51-54,58,59] The remaining thirty-six[63-98] studies were excluded for the following reasons (see figure 1): duration <8 weeks (19 studies),[63-81] the report described a substudy or a subanalysis of a trial that had already been included (eight studies),[82-89] they were uncontrolled or non-randomised (seven studies)[90-96] or the authors did not respond to the request of information on the group from which withdrawals occurred (two studies).[97,98]

There were twenty-two (43%) trial reports[13,16,18,20,21,25-27,32,34,36-39,44,47,49-51,55,61,62] that contained complete information on the number and the reasons for withdrawals. The principal investigator and/or the sponsor pharmaceutical company were contacted and asked for details on the number and reasons for withdrawals on the remaining 29 trials. Of these, a response with additional and complete information was obtained from seventeen trials.[12,14,19,23,24,29,30,33,35,40,41,43,45,46,57-59] For the remaining twelve trials,[15,17,22,28,31,42,48,52-54,56,60] information was obtained only on certain variables, and therefore they were only included in the analyses of the variables for which information was given in the respective reports (see figure 1).

Baseline Patients' Characteristics and Primary Endpoints

A total of 18 234 patients were studied, 78.7% of whom were male. Of these, 9668 were randomised to receive an ACE inhibitor, and 8566 to the refer-

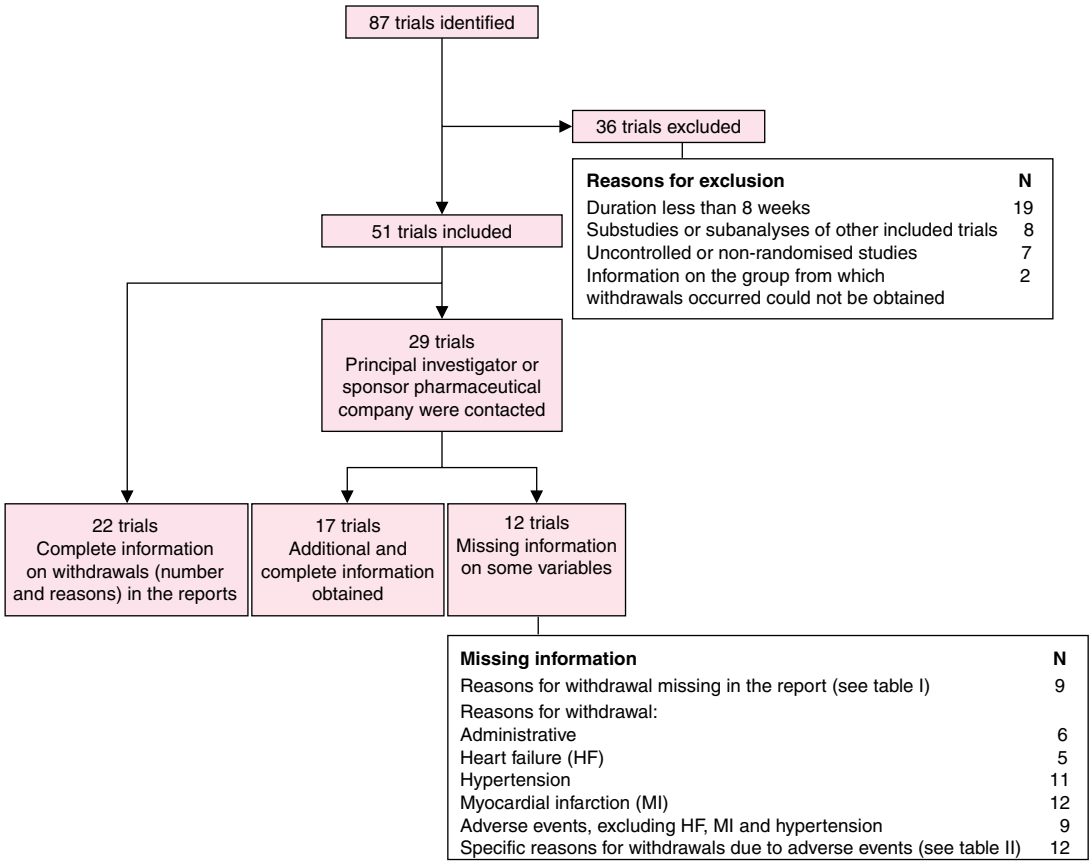

Fig. 1. Clinical trials of ACE inhibitors in the treatment of heart failure and ventricular dysfunction after myocardial infarction. **N** = number of trials.

ence treatment. The mean age varied from 49 to 82 years; the weighted mean age for the patients included in the meta-analysis was 61.8 years. The mean duration of the trials was 29.2 weeks (SD ± 5.8), and the median was 12 weeks (range 8–180); the corresponding weighted mean duration was 100.2 weeks per patient. Enalapril was evaluated in 12 trials (7311 patients),[14,16,17,20,30,42-45,47,49,62] captopril in nine (3033 patients),[28,32-34,36,37,39,50,56] ramipril in six (2894 patients),[23,51-54,60] trandolapril in one (1749 patients),[24] and quinapril in six (935 patients).[27,29,40,41,58,59] Other ACE inhibitors were cilazapril (six trials, 617 patients),[18,38,55-57,61] fosinopril (two trials, 549 patients),[12,19] lisinopril (three trials, 337 patients),[21,22,31] perindopril (three trials, 252 patients),[25,26,48] benazepril (two trials, 232 patients),[15,46] delapril (one trial, 101 patients),[13] and zofenopril (one trial, 24 patients).[35] All but three[34,46,57] trials (125 patients), were double-blind and placebo-controlled. In 24 trials the primary endpoint was exercise tolerance,[12,15,17-20,22,23,27,29,31-33,41,42,44,49,52-56,61,62] in 11 the effect on haemodynamic variables and/or biochemical measurements,[13,21,26,34,37,38,40,46,47,50,57] in nine the effect on the NYHA functional class,[14,16,25,35,39,48,51,58,59] and in seven total mortality.[24,28,30,36,43,45,60] In sixteen trials[12,16,18,20,24,28-30,33,35,37,39,43,45,52,54] (13 076 patients) a run-in phase with an ACE inhibitor had to be completed, or a test dose was given before

randomisation; during these phases, 416 patients (3.2%) were excluded because of adverse events or non-compliance.

The majority of the randomised patients (53.3%) were in NYHA functional class II or III, 36.7% in class I or asymptomatic, and 3% in class IV; no information was given on the functional class for the remaining 7%. The mean ejection fraction varied among studies from 14% to 62%. In the trial reports giving information on concomitant treatments, 53.6% of patients received diuretic treatment (29 trials), 34.6% received digitalis (29 trials), 17.1% β-adrenoceptor antagonists (38 trials), 25.5% calcium channel antagonists (36 trials), and 6.5% hydralazine (32 trials), with similar distribution in both arms (ACE inhibitors and control).

Withdrawals and Reasons for Withdrawal

The withdrawal rate was 24.3% (2348/9668) among patients allocated to ACE inhibitors, and 27.8% (2383/8566) among those allocated to the reference treatment (see table I). Each patient could have been withdrawn for more than one reason, and there were 2774 reasons for withdrawal among those allocated to ACE inhibitors, and 2910 among those in the control groups. There were 1213/7668 withdrawals for administrative reasons among patients randomised to treatment with ACE inhibitors, and 1281/7152 among those in the control groups. Withdrawals due to worsening of CHF were 543/8672 with ACE inhibitors, and 952/8134 in the control groups (RR = 0.54; 95% CI 0.46–0.63), those due to myocardial infarction were 41/6191 with ACE inhibitors and 66/5798 in the control groups (RR = 0.64; 95% CI 0.43–0.93), and those due to hypertension were 14/7306 among patients treated with ACE inhibitors and 43/6914 among those in the control groups (RR = 0.37, 95% CI 0.20–0.67). The remaining reasons for withdrawal were more common among patients allocated to ACE inhibitors (1035/7487, 13.8 per 100 patients) than among those allocated to the reference treatment (661/7025, 9.4 per 100 patients; weighted difference of 3.1% [95% CI, 1.8–4.4%], RR = 1.54, 95% CI, 1.30–1.83) [see table I]. Therefore, for each of the 32 patients treated with an ACE inhibitor during a mean of 100.2 weeks, one additional treatment withdrawal due to an adverse event occurred. No heterogeneity among the trials regarding withdrawals due to adverse events related to ACE inhibitors was seen ($\chi^2 = 37.25$, $p = 0.14$).

By organs and systems, the most common adverse events leading to treatment withdrawal were respiratory (RR = 1.86; 95% CI 1.40–2.49), renal (RR = 2.03; 95% CI 1.55–2.67), reproductive (RR = 6.46; 95% CI 1.14–36.58), and general (RR = 1.27;

Table I. Number of withdrawals and main reasons for patient withdrawal in trials of ACE inhibitors in the treatment of heart failure and ventricular dysfunction after myocardial infarction

Variable	ACE inhibitors withdrawals		Reference treatment withdrawals	
	no./total no. of patients	rate per 100 patients	no./total no. of patients	rate per 100 patients
Number of patients withdrawn	2348/9668	24.3	2383/8566	27.8
Number of reasons for withdrawal[a]	2774/7487	37.0	2910/7025	41.4
Reason for withdrawal				
administrative reason	1213/7668	15.8	1281/7152	17.9
heart failure	543/8672	6.3	952/8134	11.7
hypertension	14/7306	0.2	43/6914	0.6
myocardial infarction	41/6191	0.7	66/5798	1.1
adverse events, excluding heart failure, myocardial infarction and hypertension	1035/7487	13.8	661/7025	9.4

a A patient could be withdrawn for more than one reason.

Table II. Main reasons for adverse event-related withdrawals in clinical trials of ACE inhibitors in the treatment of heart failure and ventricular dysfunction after acute myocardial infarction

Adverse event	Number of withdrawals		RR (95% CI)
	ACE inhibitors (n = 6191)	reference treatment (n = 5798)	
Respiratory (total)	137	66	1.86 (1.40–2.49)
cough	123	34	3.19 (2.22–4.57)
dyspnoea	4	13	0.38 (0.13–1.08)
pulmonary oedema	7	8	0.90 (0.33–2.42)
other known	0	1	0.11 (0.00–2.75)
other unknown	3	10	0.30 (0.08–1.08)
Cardiovascular (total)	182	128	1.26 (1.01–1.58)
hypotension	102	45	1.95 (1.39–2.74)
angina	21	17	1.02 (0.53–1.97)
rhythm disturbances	7	11	0.59 (0.23–1.47)
other known	43	47	0.88 (0.58–1.31)
other unknown	9	8	1.12 (0.43–2.89)
Renal (total)	155	73	2.03 (1.55–2.67)
renal dysfunction	59	31	1.84 (1.20–2.81)
renal failure	8	2	3.35 (0.81–13.80)
creatinine increase	24	7	2.88 (1.28–6.52)
urea increase	57	25	2.23 (1.37–3.65)
other known	5	5	0.96 (0.28–3.24)
other unknown	2	3	0.66 (0.11–3.97)
Metabolism and endocrinological (total)	30	12	3.10 (0.89–10.78)
hyperkaliaemia	22	2	7.11 (2.11–23.94)
other known	2	0	3.07 (0.32–29.32)
other unknown	6	10	0.60 (0.22–1.64)
Gastrointestinal (total)	52	48	1.02 (0.69–1.51)
nausea or vomiting	32	25	1.21 (0.72–2.04)
other known	5	2	1.31 (0.46–3.68)
other unknown	15	21	0.71 (0.37–1.37)
Cutaneous (total)	36	28	1.20 (0.73–1.95)
rash	20	19	1.06 (0.56–2.00)
angioedema	8	5	1.50 (0.53–4.20)
pruritus	3	1	1.58 (0.24–10.49)
other known	2	1	0.69 (0.10–4.90)
other unknown	3	2	1.49 (0.25–8.92)
General (total)	177	136	1.27 (1.02–1.58)
dizzines	92	56	1.60 (1.15–2.23)
fatigue	53	44	1.20 (0.81–1.79)
other known	5	6	0.60 (0.21–1.73)
other unknown	27	30	0.90 (0.54–1.50)
Sensory organs (total)	22	13	1.43 (0.71–2.87)
dysgeusia	14	8	1.75 (0.73–4.19)
other known	4	5	0.71 (0.17–2.97)

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Table II. Contd

Adverse event	Number of withdrawals		RR (95% CI)
	ACE inhibitors (n = 6191)	reference treatment (n = 5798)	
other unknown	4	0	8.97 (0.48–166.35)
Nervous system (total)	29	43	0.67 (0.42–1.07)
cerebrovascular accident	17	20	0.87 (0.46–1.67)
headache	4	7	0.61 (0.19–1.96)
other known	1	2	0.33 (0.04–2.67)
other unknown	7	14	0.50 (0.20–1.23)
Musculoskeletal	1	2	0.61 (0.08–4.85)
Collagen disease	1	0	3.14 (0.13–76.08)
Psychiatric[a]	1	5	0.34 (0.06–1.99)
Reproductive[b]	10	1	6.46 (1.14–36.58)
Haematological	7	2	2.05 (0.60–7.02)
Cancer	3	3	1.07 (0.22–5.09)
Non cardiac surgery	9	17	0.55 (0.25–1.21)

a Depression in all cases.

b Impotence in all cases.

RR = relative risk.

95% CI 1.02–1.58) [see table II]. The specific adverse events leading to a higher withdrawal rate among those allocated to ACE inhibitors compared with those allocated to the reference treatment were cough (2% vs 1.1%; RR = 3.19; 95% CI 2.22–4.57), hypotension (1.6% vs 0.8%; RR = 1.95; 95% CI 1.39–2.74), dizziness (1.5% vs 0.9%; RR = 1.60; 95% CI 1.15–2.23), renal dysfunction (0.9% vs 0.5%; RR = 1.84; 95% CI 1.20–2.81), uraemia (0.9% vs 0.4%; RR = 2.23; 95% CI 1.37–3.65), increase in serum creatinine level (0.4% vs 0.1%; RR = 2.88; 95% CI 1.28–6.42), hyperkalaemia (0.4% vs 0.03%; RR = 7.11; 95% CI 2.11–23.94), and impotence (0.2% vs 0.02%; RR = 6.46; 95% CI 1.14–36.58).

The specific administrative reasons that led to a higher withdrawal rate were patient' decision (5.8% among those allocated to ACE inhibitors and 5.6% among those allocated to the reference treatment), recommendation by physician and/or nurse (5.2% and 7.7%, respectively), and protocol violation and lack of adherence (1.6% and 0.5% among those allocated to ACE inhibitors and 1.5% and 0.5% among those in the reference groups, respectively).

In order to assess the potential influence of missing data from the trials excluded from the analysis, a reanalysis was performed where these trials were included assuming no additional risk of withdrawal with ACE inhibitors (RR of 1 for each trial). In this reanalysis, the risk of withdrawal due to adverse events excluding worsening CHF, myocardial infarction and hypertension (RR = 1.44; 95% CI 1.24–1.66) was still higher among patients allocated to ACE inhibitors compared with those allocated to the reference treatment. With these results for every 48 treated patients during a mean of 100.2 weeks, one additional adverse event leading to treatment withdrawal occurs.

Figure 2 shows the relation between the size of the trials and the difference in the withdrawal rates between both treatment groups. Trials of smaller size were equally distributed in both sides of the summary estimate of the effect.

Table III shows the information given on target daily doses and those actually taken in the trials with enalapril and in the main trials with captopril, ramipril and trandolapril. In the majority of reports

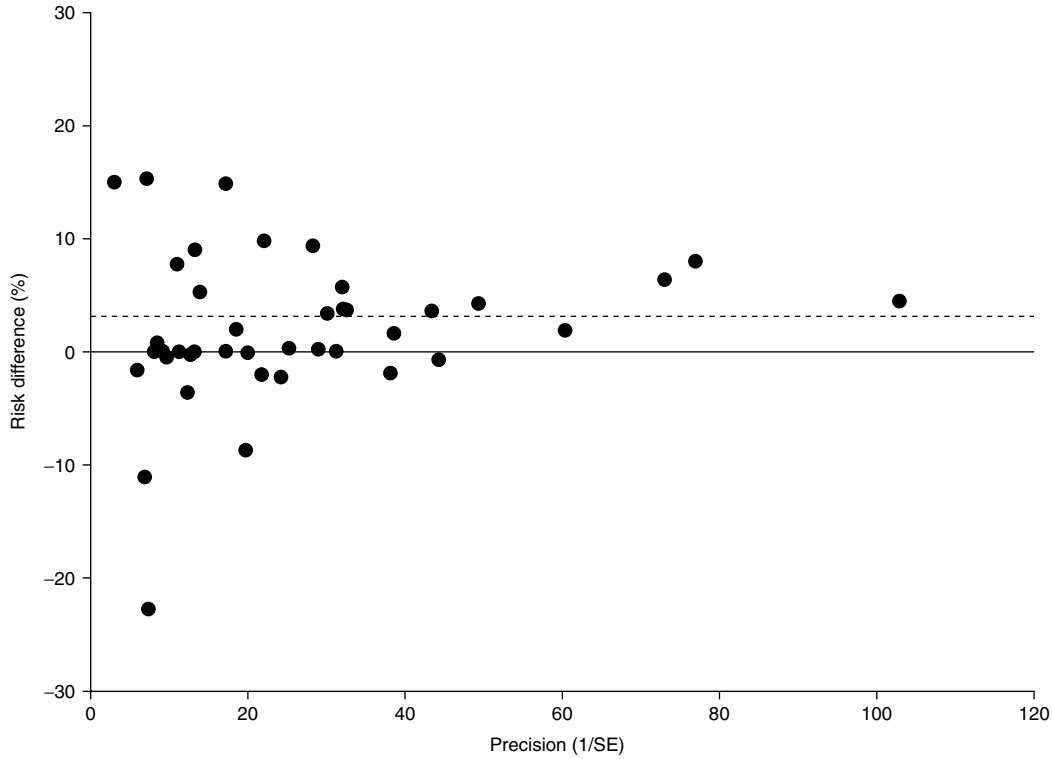

Fig. 2. Funnel plot of risk differences according to precision (inverse of the standard error [SE]) of estimate in each trial.

this information was scarce. For this reason the effect of dose could not be analysed.

Discussion

This is the first published meta-analysis of adverse events associated with to ACE inhibitors in patients with CHF and/or ventricular dysfunction. It is also the largest study on this issue, in terms of number of patients. Apart from worsening of CHF, which was, as expected, the main cause leading to treatment withdrawal, the withdrawal rate attributed to adverse events was higher among patients allocated to ACE inhibitors, compared with those allocated to the reference treatment. Our results suggest that treating 32 patients for 2–45 months gives rise to one additional adverse event leading to treatment withdrawal. This should be considered favourable, when compared with the magnitude of the therapeutic effect of ACE inhibitors in the treatment of CHF estimated in recent meta-analyses, which indicate that by treating 15 or 10 patients for between 3 and 42 months avoids, respectively, one death or one hospital admission because of worsening CHF.[99,100]

In the present study the rate of withdrawals due to adverse events among patients allocated to ACE inhibitors was 13.8% after excluding hypertension and myocardial infarction (see table I). This figure is fairly similar to the 15.2% rate seen in the SOLVD studies subanalysis.[7] However, the duration of the SOLVD trials was longer (40 months) than the mean duration of the trials included in the present meta-analysis.

The adverse effects associated with ACE inhibitor use that most frequently lead to treatment withdrawal were cough, hypotension and dizziness; oth-

er events were azotaemia, hyperkalaemia, and impotence. Although the data regarding impotence were contributed mostly by the SOLVD trials, whose authors considered them as a fortuitous finding, our results support the growing view that impotence is a rare adverse event of ACE inhibitors.[101,102] The mechanism of ACE inhibitor-induced impotence is unknown, although a reduction of peripheral vascular resistance has been suggested.[101] Similarly to the findings of the SOLVD studies subanalysis, withdrawals due to angioedema were rare.[7]

Publication bias is a potential limitation in meta-analysis of clinical trials. Although this cannot be ruled out, we believe that publication bias is unlikely, because the funnel plot did not suggest any difference or trend of the results of small trials, compared with those of larger trials (figure 2).

It was not possible to include the results of a low proportion of trials in the analysis of some of the variables, because the information was unavailable. However, had the excluded trials shown no additional risk (i.e. the risk of withdrawal due to an adverse event is the same among those allocated to ACE inhibitors and those allocated to placebo), the final result would have been significant and relevant – treating 48 patients with an ACE inhibitor during a mean of 25 months would result in one withdrawal due to an adverse event.

Similarly, it was not possible to evaluate the incidence of all adverse events related to ACE inhibitors, and not only those leading to treatment withdrawal, because this information was unavailable and because of heterogeneity in data collection methods. However, we believe that adverse drug events leading to treatment withdrawal are those clinically more relevant, and that this is the most adequate variable which should be compared with the beneficial effect of these drugs in terms of a decrease in mortality and in the rate of hospital admission.

The main limitation of our study arises from the limited external validity of clinical trials. Patients included in clinical trials differ from those in usual practice, in terms of age and sex,[103] doses prescribed and taken,[104-107] comorbidity, duration of use, and diagnostic procedures.[103] In our meta-analysis, women comprised only 20% of the study population, while in a series of adverse events of

Table III. Information about the dose in the clinical trials with enalapril and in the main trials with captopril, ramipril and trandolapril

ACE inhibitor	No. of patients allocated to ACE inhibitors	Target daily dose (mg)	Mean daily dose in patients allocated to ACE inhibitors (mg)	Patients who achieved the target dose (%)	Reference
Enalapril	10	40	NA	85	14
Enalapril	11	40	NA	36	16
Enalapril	20	20	18.75	NA	17
Enalapril	9	20	NA	11	20
Enalapril	127	40	18.4	28	30
Enalapril	48	10	NA	NA	42
Enalapril	1285	20	16.6	49.3	43
Enalapril	8	10	NA	NA	44
Enalapril	2111	20	16.7	56.1	45
Enalapril	21	20	NA	90	47
Enalapril	18	10	NA	NA	49
Enalapril	11	40	NA	NA	62
Captopril	1115	150	NA	79	28
Ramipril	1004	10	NA	77	60
Trandolapril	876	4	NA	NA	24

NA = not available.

ACE inhibitors from routine clinical practice women account for more than 50% of cases,[108,109] and the risk of certain adverse events, such as cough, is higher among women.[108,109] Similarly, the mean age of patients in this meta-analysis was 61.8 years, while the mean age of patients in series of routine practice has been 76 years[103] and 74 years.[110] It has been suggested that tolerability of ACE inhibitors would be less in usual clinical practice, and this may have led, at least in part, to their underuse and to the use of lower than recommended doses in patients with CHF.[104-107] In this respect, evaluation of the effect of the dose on the rate of withdrawals attributed to adverse events would have given important information, but in the published reports data on the actual taken by patients was scarce (see table III), and the effect of dose could not be evaluated.

Finally, the present meta-analysis uncovers several limitations regarding the publication of safety information in the reports on clinical trials. It has been stressed that information on adverse events given in reports of clinical trials is inadequate,[111-115] and that this prevents the systematic evaluation of the risks of therapeutic interventions.

With the aim of guaranteeing minimal information standards on these issues, investigators, institutions (such as Ethics Committees and international agencies), and medical editors should agree and apply criteria for the ascertainment, terminology and classification, severity assessment, and publication of adverse events in clinical trials. The aim should be a better appraisal of the benefit-risk ratio of therapeutic interventions. This should facilitate estimation of the incidence of the most relevant adverse events (and in particular of those leading to treatment withdrawal), and comparing the incidence and pattern of adverse events in clinical trials with those seen in routine practice. The last version of the CONSORT guidelines on reporting the results of clinical trials recommended providing estimates of the frequency of the main severe adverse events and reasons for treatment discontinuations separately for each intervention group.[116] However, to make the safety data from clinical trials more useful in daily practice, the collection of safety information in clinical trials must be improved by means of active surveillance with predefined structured questionnaires, classification by organs and systems and by severity, a full specification of adverse events per study arm, and a detailed description of the adverse events which are unusual or which have not been previously described.

Conclusions

Among patients enrolled in randomised clinical trials on CHF or ventricular dysfunction, starting an ACE inhibitor leads to an additional 3% of treatment withdrawals due to adverse events during a mean observational period of 100 weeks. In a significant proportion of the reports on these randomised clinical trials, information on adverse events leading to treatment withdrawal was inadequate. With the aim of guaranteeing minimal information standards on these issues, investigators, institutions and medical editors should agree and apply criteria for the ascertainment, terminology and classification, severity assessment, and publication guidelines of adverse events in clinical trials.

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Correspondence and offprints: Dr *Joan-Ramon Laporte*, Fundació Institut Català de Farmacologia, Servei de Farmacologia Clínica, Hospital Vall d'Hebron, P Vall d'Hebron 119-129, 08035-Barcelona, Spain.
E-mail: jrl@icf.uab.es